

A low distribution volume as a determinant of efficacy and safety for histamine (H_1) antagonists

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The method used to define the basis of a new classification of a well-known pharmacologic class requires the selection of drugs according to their respective potencies. However, in the case of the H_1 -antagonists, many drugs in current use, particularly those belonging to the second generation of antihistamines, are already well recognized as being very effective treatments in allergic diseases. Progress with this class of drugs might therefore involve not only increased efficacy, but also improvements in their safety and specificity. Because these drugs are often used to treat non-life-threatening conditions such as allergic rhinitis, consideration of their benefit/risk ratio is of great importance.

Severe side-effects of several compounds of this class have been described, but these are rare and most of them are related to overdose. These side-effects involve cardiac or hepatic effects and may be due to drug accumulation in the heart or liver (1-3). Cetirizine, unlike terfenadine or astemizole, has not been associated with any adverse cardiovascular effects. Furthermore, administration of cetirizine (20 or 60 mg/day) for 7 days to healthy volunteers did not prolong the Q-Tc interval of electrocardiograph recordings, as compared with placebo (4). Various adverse effects have been reported in special circumstances; for example, elimination of cetirizine in the elderly may be prolonged, an effect that is dependent on impaired renal function in these subjects (5). Although antihistamines are often taken in combination with various other drugs, notably decongestants and analgesics, toxic reactions are surprisingly rare (6, 7). The main side-effect of this class of drugs remains sedation, particularly because these drugs are given to patients with chronic disorders, and treatment can therefore often extend over a period of several months. Thus, while H_1 -antagonism efficacy must be maintained, drug accumulation in

inappropriate tissues must be avoided or decreased. In other words, the pharmacologic targets, i.e., the H_1 -receptors, must be separated from toxic sites, because they are found in different locations or are stimulated at other, usually higher, drug concentrations. Another question which arises is, do we have objective arguments, apart from direct observations, which allow us to select one member of the second-generation antihistamines on the grounds that it is safer, i.e., has a better benefit/risk ratio, than the other drugs available?

Several H_1 -antagonists have a low distribution volume (V_D) and this property may be a real advantage. Various definitive characteristics of the ideal H_1 -antagonist may be proposed. Some of the requirements which would optimize the body distribution of an H_1 -receptor antagonist would include limitation to the targeted receptors, and drug concentrations high enough to counteract released histamine and to prevent further histamine release from mast cells and basophils. Such a drug would have a distribution limited to the H_1 -receptors. These receptors have a wide cellular distribution, being found on smooth-muscle cells, endothelial cells, mast cells, basophils, and eosinophils (8). It is interesting to note that all these receptors are easily reached from the blood, because they are either in direct contact with it, as are endothelial cells, or very close to it and thus readily accessible, as are the vascular smooth-muscle cells.

Therefore, an H_1 -antagonist does not need an extensive tissue distribution as part of its mode of action. The H_1 -receptor, or recognition site, is linked to the transduction system via its G proteins, and the amplification process is provided by phospholipase C. This catalyzes the formation of inositol phosphates, e.g., inositol triphosphate (IP3), inside the cell. IP3 initiates the release of calcium from intracellular stores. Another product of phospholipase C action, i.e., diacylglycerol

(DAG), activates protein kinase C. This can up-regulate or downregulate the signal from raised calcium levels (released from intracellular stores) via the phosphorylation it produces. In some cases, calcium influx constitutes the effector response, entering via receptor-operated calcium channels. The channel is opened by a G-protein linked to the ligand-receptor interaction. In the case of mast cells or basophils, the net result of this process is the release of mediators, particularly histamine. Since the target of the H₁-antagonist is an external receptor, the pharmacologic effect is achieved without cell penetration, there being no need for the drug to cross the cell membrane or reach the cytosol.

Fig. 1 shows the quantitative distribution of H₁-receptors in the body and highlights the receptors which have to be reached. The main problem is that posed by brain receptors because they are numerous, constituting about 40% of the total number of H₁-receptors (9). Ideally, H₁-antagonists would not reach these receptors; i.e., they would be unable to cross the blood-brain barrier. Drugs which have a relatively high liposolubility are thought to cross the blood-brain barrier by a process of passive transport. It is obviously desirable to prevent the interaction of antihistamines with the H₁-receptors of the brain. However, it is impossible to prevent all contact with them, especially with those of endothelial cells, although brain transfer can be drastically limited (10). The same considerations apply to heart receptors because it is impossible to prevent contact with receptors of heart vessels, but it is possible to inhibit drug penetration at appropriate dosages.

All these considerations can be summarized in pharmacokinetic terms in that an H₁-antagonist must have a low distribution volume, less than that of the volume of exchangeable water in the body. Exchangeable water may be defined as that water

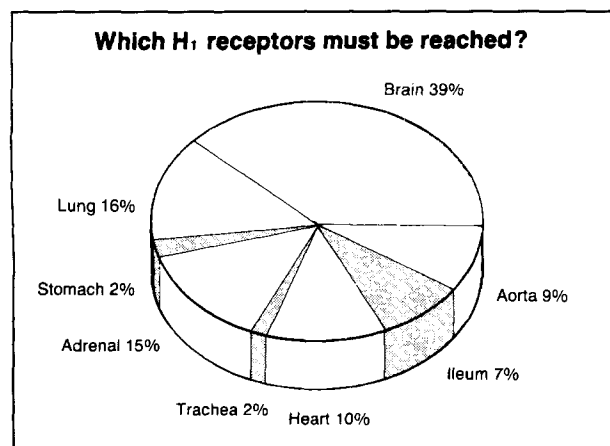


Fig. 1. Which H₁-receptors must be reached?

which is freely and quickly exchanged between extracellular fluids and cytosol. It must be distinguished from the constitution water which is bound to cell components, especially to proteins. Assessment with antipyrine has shown that the volume of exchangeable water is 0.6 l/kg (11). As mentioned above, H₁-antagonists do not have to reach the cytosol; thus, their distribution volumes may be, at the very most, 0.6 l/kg, but, by more accurate measurement, this figure may prove to be much less. At such a low V_D , crossing of the blood-brain barrier would be minimized. In addition, under these conditions, liver metabolism would not be a factor in the variability of the effect of H₁-antagonists among subjects, and intracellular transfer would not be a problem. Unlike various other antihistamines, cetirizine is not metabolized in the liver, but is excreted in urine and feces as unchanged drug (12).

The possible variations in the apparent distribution volumes of several drugs are shown in Fig. 2. The lowest V_D we can detect is about 0.1 l/kg. Generally, this indicates that the drug is "tightly" bound to human serum albumin (HSA). Indeed, the V_D of injected HSA is 0.1 l/kg: this tells us that the protein has a high association constant for such a drug, higher than those observed in tissues. Thus, the drug distribution is restricted to the lone distribution compartment of its binding protein.

Table 1 shows the pharmacokinetic variables of cetirizine in man. Clearly, the V_D is low, ranging from 0.4 to 0.6 l/kg. To my knowledge, cetirizine is the only H₁-antagonist to exhibit such a low distri-

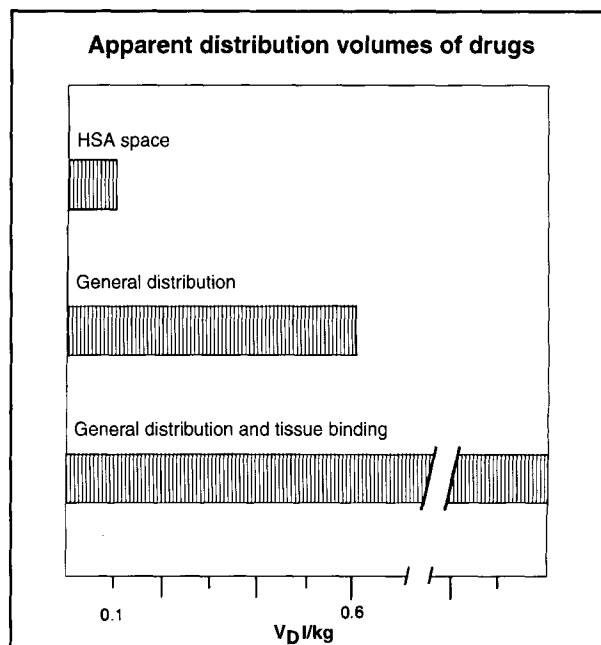


Fig. 2. Apparent distribution volumes of drugs. HSA: human serum albumin.

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Table 1. Cetirizine pharmacokinetics in man

V_D in $\text{l} \cdot \text{kg}^{-1}$	0.4–0.6
Plasma binding (%)	88–90
Elimination clearance	0.6 ml/min per kg
Renal elimination	70% (unchanged at 72 h)
Half-life	10 h

Table 2. Binding parameters of cetirizine

	Saturable bindings	
	n	K_a (M^{-1})
HSA	1.78 ± 0.14	9780 ± 13
AAG	1.74 ± 0.67	5125 ± 24
	Nonsaturable bindings	
	n	K_a (M^{-1})
HDL	$75\,000 \pm 575$	
LDL	$221\,000 \pm 9100$	
VLDL	$290\,000 \pm 25\,000$	
GG	NS	
Erythrocytes	4.28 ± 0.19	

n : number of binding sites; K_a : association constant in M^{-1} ; HSA: human serum albumin; AAG: α_1 -acid glycoprotein; HDL, LDL, and VLDL: lipoproteins; GG: gamma globulins.

Table 3. Pharmacokinetic parameters of some H_1 antagonists

	$T_{1/2\beta}$ in h	B %	V_D l/kg
Chlorpheniramine	22 ± 6.0	69–72	5.9 ± 0.9
Brompheniramine	24.9 ± 9.3	72	2.5–10
Triprolidine	30	90	8.7 ± 7.8
Hydroxyzine	20.0 ± 4.0		16.0–30.5
Diphenhydramine	31.05	85–98	3.3
Astemizole	26	96.7	48
Azelastine	25		*
Ebastine	10–12		
Levocabastine	35–40	55	
Loratadine	12 ± 4	97	*
Terfenadine	16–23	98	2.2–2.9
Cetirizine	10	88–90	0.5

$T_{1/2\beta}$: elimination half-life; B %: drug bound in plasma in %; V_D : apparent distribution volume in l/kg (weight).

* Data not available.

bution volume, and I feel that this is the main explanation of its safety. Moreover, animal studies in several species have shown that peak cetirizine tissue concentrations are less than 10% of the plasma concentration (13). Thus, distribution of cetirizine is poor in tissues and organs, with the result that in these areas its concentrations are always low, a fact which in turn minimizes the risk of dose-dependent side-effects. One obvious explanation of the low V_D of cetirizine is its plasma binding. Fig. 3 summarizes this property, from which three main points arise:

- 1) Cetirizine is extensively bound in blood (unbound fraction = 5%).
- 2) Cetirizine is principally bound by HSA (B = 73%).
- 3) Red blood cells and lipoproteins bind only a small amount of the drug.

Thus, the combination of a high binding percentage with a low distribution volume allows one to conclude that plasma binding impairs extensive tissue distribution by retaining the drug in the binding protein compartment. As for the binding features of cetirizine (Table 2), binding to both HSA and α_1 -acid glycoprotein (AAG) is saturable; in both cases, the number of binding sites is about two. Binding to several proteins was not saturable, probably reflecting the lipophobicity of the molecule. One interesting feature of cetirizine is that its interaction with HSA involves the two main binding sites of the protein (14): site I, or the warfarin-binding site ($K_a = 5000 \text{ M}^{-1}$), and site II, or the diazepam-binding site ($K_a = 14\,000 \text{ M}^{-1}$). Binding to these sites is generally mutually exclusive, indicating that interactions of cetirizine with other drugs may occur at the *two sites*. This low association constant may be considered to affect efficacy, because HSA binding might impair the tissue distribution of cetirizine, inhibiting access to its receptors. However, the association constant of the H_1 -receptor for cetirizine is 2500 times the plasma association constant. Unlike other antihistamines such as hydroxyzine, cetirizine is highly selective for H_1 -receptors (15). Moreover, for most H_1 -receptor antagonists, the apparent volumes of distribution and total body clearance remain large,

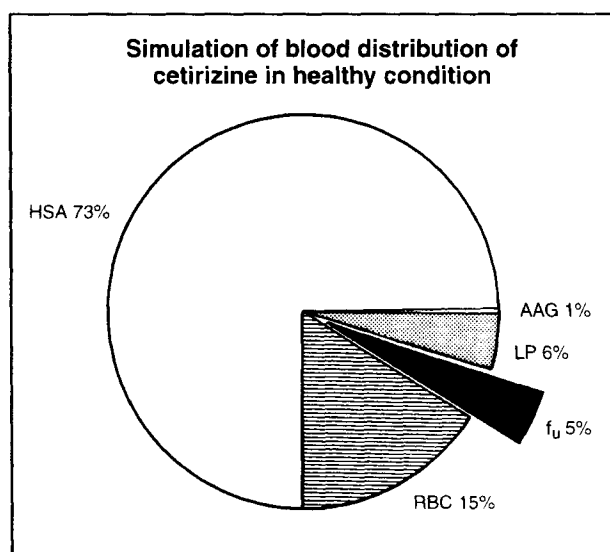


Fig. 3. Simulation of blood distribution of cetirizine in healthy condition. HSA: human serum albumin; RBC: red blood cells; LP: lipoproteins; AAG: α_1 -acid glycoprotein; f_u , unbound fraction of drug.

while cetirizine, exceptionally, shows a very low volume of distribution (16).

The pharmacokinetic features of other H₁-antagonists are shown in Table 3. It is probable that all of these drugs have a much higher V_D than cetirizine. An asterisk (*) in the table indicates that data were not available but that the corresponding drug is known to bind to tissues (higher concentrations therein than in plasma, thus exhibiting a larger V_D). It may be of interest to look for a correlation between side-effect frequencies and corresponding V_D , because most of these seem to be linked to the relative accumulation of this class of drug. What is the explanation of the large V_D of the other H₁-antagonists? As these drugs all exhibit plasma-binding effects greater than that observed with cetirizine, how can we account for the fact that such a relatively modest plasma binding is high enough to restrict tissue binding when higher plasma binding does not? Restrictive plasma binding is characterized by a binding capacity higher in plasma than in tissues. Some consequences of this are a low apparent distribution volume (<0.6 l/kg), a high plasma-binding capacity, tissue levels lower than blood levels, and low metabolic clearance. Furthermore, I hypothesize that the plasma kinetics often fit with a monocompartmental model, because of the absence of a peripheral compartment, and also because the drug dosage is concentrated in the albumin space. This feature is observed with cetirizine but not, to my knowledge, with other H₁-antagonists. What is clear is that the association constant of cetirizine to HSA is in itself not sufficient to explain its low distribution volume. Other causes probably include the ionization of the molecule, its lipophobicity, and its marked H₁-receptor specificity (17).

It is likely that the ampholytic character of cetirizine explains its poor penetration inside blood cells. Another possibility is that cetirizine recognizes only H₁-receptors, while other H₁-antagonists recognize other receptors or targets (specific and nonspecific binding). One final point on the ability of cetirizine to bind to HSA concerns the well-documented anti-inflammatory effects of this drug. Acute inflammation involves both vasodilation and increased capillary permeability, one result of which is that HSA is leached from the blood vessels into the surrounding tissues. The cetirizine-HSA complex could then be leached into the surrounding tissue. This might account for development of a swift anti-inflammatory effect by cetirizine bound to carrier HSA. As already mentioned, cetirizine has a far higher affinity for the H₁-receptor; hence, any ligand-free receptors would successfully compete for the HSA-bound cetirizine. This specificity would also limit poten-

tial side-effects through spillover action on serotonin and calcium channel blocker receptors.

In conclusion, I would like to suggest pharmacokinetic criteria for the recognition of a new generation of H₁-antagonists. These include a distribution volume low enough to bind H₁-receptors specifically, plasma binding to limit tissue transfer, no extensive liver metabolism, and a once-daily oral dosage regimen. In my opinion, the most important of these is undoubtedly a low distribution volume. At present, cetirizine is the only H₁-antagonist fulfilling this last criterion.

Round-table discussion

Juhlin: Are H₁-receptors present on the basal epithelial cells in the skin?

Tillement: Yes, they are.

Simons: What about the histamine intracellular receptor (H_{1C}), i.e., the non-H₁, -H₂, or -H₃ histamine receptor?

Tillement: I'm not sure. Could you elaborate?

Simons: There seems to be another kind of histamine receptor involved in cell growth and differentiation, possibly in neoplasia. We should, at some stage, pay more attention to it.

Broide: It seems cetirizine is more specific for H₁-receptors than other antihistamines. Do you know where the binding site is on the cetirizine molecule for histamine, compared to, say, hydroxyzine? Are the two sites different?

Tillement: No.

Simons: We still know very little about how histamine interacts or binds to its receptors at the molecular level.

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